▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Deltyba 50 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50 mg delamanid.

Excipient with known effect
Each film-coated tablet contains 100 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Round, yellow, film-coated tablet, 11.7 mm in diameter, debossed with 'DLM' and '50' on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Deltyba is indicated for use as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis (MDR-TB) in adults, adolescents and children with a body weight of at least 30 kg when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability (see sections 4.2, 4.4 and 5.1).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Treatment with delamanid should be initiated and monitored by a physician experienced in the management of multidrug-resistant *Mycobacterium tuberculosis*.

Delamanid must always be administered as part of an appropriate combination regimen for the treatment of multidrug-resistant tuberculosis (MDR-TB) (see sections 4.4 and 5.1). Treatment with an appropriate combination regimen should continue after completion of the 24-week delamanid treatment period according to WHO guidelines.

It is recommended that delamanid is administered by directly observed therapy (DOT).

Posology

Adults
The recommended dose for adults is 100 mg twice daily for 24 weeks.

Adolescents and children
Paediatric patients with a body weight of

- ≥ 30 to < 50 kg: the recommended dose is 50 mg twice daily for 24 weeks
- ≥ 50 kg: the recommended dose is 100 mg twice daily for 24 weeks

Elderly patients (> 65 years of age)
No data are available in the elderly.

Renal impairment
No dose adjustment is considered necessary in patients with mild or moderate renal impairment. There are no data on the use of delamanid in patients with severe renal impairment and its use is not recommended (see sections 4.4 and 5.2).

Hepatic impairment
No dose adjustment is considered necessary in patients with mild hepatic impairment. Delamanid is not recommended in patients with moderate to severe hepatic impairment (see sections 4.4 and 5.2).

Paediatric population
The safety and efficacy of delamanid 50 mg film-coated tablets in children with a body weight of less than 30 kg have not yet been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

Method of administration

Oral use.
Delamanid should be taken with food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Serum albumin < 2.8 g/dL (see section 4.4 regarding use in patients with serum albumin ≥ 2.8 g/dL).
- Coadministration of medicinal products that are strong inducers of CYP3A4 (e.g. carbamazepine).

4.4 Special warnings and precautions for use

There are no data on treatment with delamanid for more than 24 consecutive weeks (see section 4.2).

There are no clinical data on the use of delamanid to treat
- extra pulmonary tuberculosis (e.g. central nervous system, bone)
- infections due to Mycobacterial species other than those of the *M. tuberculosis* complex
- latent infection with *M. tuberculosis*

There are no clinical data on the use of delamanid as part of combination regimens used to treat drug-susceptible *M. tuberculosis*.

Resistance to delamanid

Delamanid must only be used in an appropriate combination regimen for MDR-TB treatment as recommended by WHO to prevent development of resistance to delamanid.

QT prolongation

QT prolongation has been observed in patients treated with delamanid. This prolongation increases slowly over time in the first 6 to 10 weeks of treatment and remains stable therafter. QTc prolongation is very closely correlated with the major delamanid metabolite DM-6705. Plasma albumin and CYP3A4 regulate the formation and metabolism of DM-6705 respectively (see Special Considerations below).

General recommendations
It is recommended that electrocardiograms (ECG) should be obtained before initiation of treatment and monthly during the full course of treatment with delamanid. If a QTcF > 500 ms is observed either before the first dose of delamanid or during delamanid treatment, treatment with delamanid should either not be started or should be discontinued. If the QTc interval duration exceeds 450/470 ms for male/female patients during delamanid treatment, these patients should be administered more frequent ECG monitoring. It is also recommended that serum electrolytes, e.g. potassium, are obtained at baseline and corrected if abnormal.

Special considerations

Cardiac risk factors
Treatment with delamanid should not be initiated in patients with the following risk factors unless the possible benefit of delamanid is considerd to outweigh the potential risks. Such patients should receive very frequent monitoring of ECG throughout the full delamanid treatment period.
- Known congenital prolongation of the QTc-interval or any clinical condition known to prolong the QTc interval or QTc > 500 ms.
- History of symptomatic cardiac arrhythmias or with clinically relevant bradycardia.
- Any predisposing cardiac conditions for arrhythmia such as severe hypertension, left ventricular hypertrophy (including hypertrophic cardiomyopathy) or congestive cardiac failure accompanied by reduced left ventricle ejection fraction.
- Electrolyte disturbances, particularly hypokalaemia, hypocalcaemia or hypomagnesaemia.
- Taking medicinal products that are known to prolong the QTc interval. These include (but are not limited to):
    - Antiarrhythmics (e.g. amiodarone, disopyramide, dofetilide, ibutilide, procainamide, quinidine, hydroquinidine, sotalol).
    - Neuroleptics (e.g. phenothiazines, sertindole, sultopride, chlorpromazine, haloperidol, mesoridazine, pimozide, or thioridazine), antidepressive agents.
    - Certain antimicrobial agents, including:
        - macrolides (e.g. erythromycin, clarithromycin)
        - moxifloxacin, sparfloxacin (see section 4.4 regarding use with other fluoroquinolones)
        - bedaquiline
        - triazole antifungal agents
        - pentamidine
        - saquinavir
    - Certain non-sedating antihistamines (e.g. terfenadine, astemizole, mizolastine).
    - Certain antimalarials with QT-prolonging potential (e.g. halofantrine, quinine, chloroquine, artesunate/amodiaquine, dihydroartemisinin/piperaquine).
- Cisapride, droperidol, domperidone, bepridil, diphemanil, probucol, levomethadyl, methadone, vinca alkaloids, arsenic trioxide.

Hypoalbuminaemia
In a clinical study, the presence of hypoalbuminaemia was associated with an increased risk of prolongation of the QTc interval in delamanid treated patients. Delamanid is contraindicated in patients with albumin < 2.8 g/dL (see section 4.3). Patients who commence delamanid with serum albumin < 3.4 g/dL or experience a fall in serum albumin into this range during treatment should receive very frequent monitoring of ECGs throughout the full delamanid treatment period.

Co-administration with strong inhibitors of CYP3A4
Co-administration of delamanid with a strong inhibitor of CYP3A4 (lopinavir/ritonavir) was associated with a 30% higher exposure to the metabolite DM-6705, which has been associated with QTc prolongation. Therefore, if co-administration of delamanid with any strong inhibitor of CYP3A4 is considered necessary it is recommended that there is very frequent monitoring of ECGs, throughout the full delamanid treatment period.

Co-administration of delamanid with quinolones
All QTcF prolongations above 60 ms were associated with concomitant fluoroquinolone use. Therefore, if co-administration is considered to be unavoidable in order to construct an adequate treatment regimen for MDR-TB it is recommended that there is very frequent monitoring of ECGs throughout the full delamanid treatment period.

Hepatic impairment

Deltyba is not recommended in patients with moderate to severe hepatic impairment (see sections 4.2 and 5.2).

Renal impairment

There are no data on the use of delamanid in patients with severe renal impairment and its use is not recommended (see sections 4.2 and 5.2).

Paradoxical drug reaction

Post-marketing cases of paradoxical drug reactions (clinical or radiological worsening of existing lesions or development of new lesions in a patient who had previously shown improvement with appropriate antimycobacterial treatment) have been reported with Deltyba. Paradoxical drug reactions are often transient and should not be misinterpreted as failure to respond to treatment. If a paradoxical response is suspected, continuation of planned combination therapy is recommended and symptomatic therapy to suppress the exaggerated immune reaction should be initiated if necessary (see section 4.8).

Excipients

Deltyba film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on delamanid

Cytochrome P450 3A4 inducers
Clinical drug-drug interactions studies in healthy subjects indicated a reduced exposure to delamanid, of up to 45% following 15 days of concomitant administration of the strong inducer of cytochrome P450 (CYP) 3A4 (rifampicin 300 mg daily) with delamanid (200 mg daily). No clinically relevant reduction in delamanid exposure was observed with the weak inducer efavirenz when administered at a dose of 600 mg daily for 10 days in combination with delamanid 100 mg twice daily.

Anti-HIV medicinal products
In clinical drug-drug interaction studies in healthy subjects, delamanid was administered alone (100 mg twice daily) and with tenofovir disoproxil (245 mg daily) or lopinavir/ritonavir (400/100 mg daily) for 14 days and with efavirenz for 10 days (600 mg daily). Delamanid exposure remained unchanged (< 25% difference) with anti-HIV medicinal products tenofovir disoproxil and efavirenz but was slightly increased with the combination anti-HIV medicinal products containing lopinavir/ritonavir.

Effects of delamanid on other medicinal products

In-vitro studies showed that delamanid did not inhibit CYP450 isozymes.
In-vitro studies showed that delamanid and metabolites did not have any effect on the transporters MDR1(p-gp), BCRP, OATP1, OATP3, OCT1, OCT2, OATP1B1, OATP1B3 and BSEP, at concentrations of approximately 5 to 20-fold greater than the C_{max} at steady state. However, since the

concentrations in the gut can potentially be much greater than these multiples of the C_{max}, there is a potential for delamanid to have an effect on these transporters.

Anti-tuberculosis medicinal products
In a clinical drug-drug interaction study in healthy subjects, delamanid was administred alone (200 mg daily) and with rifampicin/isoniazid/pyrazinamide (300/720/1800 mg daily) or ethambutol (1100 mg daily) for 15 days. Exposure of concomitant anti-TB drugs (rifampicin [R]/ isoniazid [H]/ pyrazinamide [Z]) was not affected. Co-administration with delamanid significantly increased steady state plasma concentrations of ethambutol by approximately 25%, the clinical relevance is unknown.

Anti-HIV medicinal products
In a clinical drug-drug interaction study in healthy subjects, delamanid was administred alone (100 mg twice daily) and tenofovir disoproxil (245 mg daily), lopinavir/ritonavir (400/100 mg daily) for 14 days and with efavirenz for 10 days (600 mg daily). Delamanid given in combination with the anti-HIV-medicines, tenofovir disoproxil, lopinavir/ritonavir and efavirenz, did not affect the exposure to these medicinal products.

Medicinal products with the potential to prolong QTc
Care must be taken in using delamanid in patients already receiving medicinal products associated with QT prolongation (see section 4.4). Co-administration of moxifloxacin and delamanid in MDR-TB patients has not been studied. Moxifloxacin is not recommended for use in patients treated with delamanid.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of delamanid in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).
Deltyba is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is unknown whether delamanid/metabolites are excreted in human milk. Available pharmacokinetic/toxicological data in animals have shown excretion of delamanid and/or its metabolites in milk (for details see section 5.3). A risk to the newborns/infants cannot be excluded. It is recommended that women should not breastfeed during treatment with Deltyba.

Fertility

Deltyba had no effect on male or female fertility in animals (see section 5.3). There are no clinical data on the effects of delamanid on fertility in humans.

4.7 Effects on ability to drive and use machines

Deltyba is expected to have a moderate influence on the ability to drive and use machines. Patients should be advised not to drive or use machines if they experience any adverse reaction with a potential impact on the ability to perform these activities (e.g. headache is very common and tremor is common).

4.8 Undesirable effects

Summary of the safety profile

The most frequently observed adverse drug reactions in patients treated with delamanid + Optimised Background Regimen (OBR) (i.e. incidence > 10%) are nausea (32.9%), vomiting (29.9%), headache

(28.4%), sleep disorders and disturbances (28.2%), dizziness (22.4%), gastritis (15.9%) and decreased appetite (13.1%).

Tabulated list of adverse reactions

The list of adverse drug reactions and frequencies are based on the results from 2 double-blind placebo controlled clinical trials and on spontaneous reports. The adverse drug reactions are listed by MedDRA System Organ Class and Preferred Term. Within each System Organ Class, adverse reactions are listed under frequency categories of very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table: Adverse drug reactions to delamanid

System Organ Class	Frequency very common	Frequency common	Frequency uncommon	Frequency not known
Endocrine disorders	-	Hypothyroidism[a]	-	-
Metabolism and nutrition disorders	Decreased appetite	-	-	-
Psychiatric disorders	Sleep disorders and disturbances[b]	Psychotic disorder[c] Anxiety[d] Depression[e] Hallucination[f]	-	-
Nervous system disorders	Dizziness Headache[g]	Hypoaesthesia Tremor	Lethargy	-
Cardiac disorders	-	Atrioventricular block first degree Ventricular extrasystoles Palpitations	-	-
Respiratory, thoracic and mediastinal disorders	-	Throat irritation	-	-
Gastrointestinal disorders	Nausea Vomiting Gastritis[h]	Dyspepsia	-	-
Musculoskeletal and connective tissue disorders	-	Muscular weakness Muscle spasms	-	-
General disorders and administration site conditions	-	Chest pain	-	Paradoxical drug reaction
Investigations	-	Cortisol increased[i] Electrocardiogram QT prolonged	-	-

Event terms that represent the same medical concept or condition were grouped together and reported as a single adverse drug reaction in Table 'Adverse drug reactions to delamanid'. Preferred terms actually reported in the double-blind clinical trials and contributing to the relevant adverse drug reaction are indicated in parentheses, as listed below:

a. Hypothyroidism (hypothyroidism, primary hypothyroidism)

b. Sleep disorders and disturbances (initial insomnia, insomnia, sleep disorder, nightmare)

c. Psychotic disorder (acute psychosis, psychotic disorder, reactive psychosis, substance-induced psychotic disorder)
d. Anxiety (anxiety, anxiety disorder, generalised anxiety disorder)
e. Depression (adjustment disorder with depressed mood, depressed mood, depression, major depression, mixed anxiety and depressive disorder, persistent depressive disorder, schizoaffective disorder depressive type)
f. Hallucination (hallucination; hallucination, auditory; hallucination, visual; hallucination tactile; hallucination mixed; hypnopompic hallucination; hypnagogic hallucination)
g. Headache (head discomfort, headache, migraine, sinus headache, tension headache, vascular headache)
h. Gastritis (chronic gastritis, gastritis, gastritis erosive)
i. Cortisol increased (Cushing's syndrome, hyperadrenocorticism, cortisol increased)

Description of selected adverse reactions

ECG QT interval prolongation
In patients receiving 200 mg delamanid total daily dose in the phase 2 and 3 trials, the mean placebo corrected increase in QTcF from baseline ranged from 4.7 - 7.6 ms at 1 month and 5.3 ms - 12.1 ms at 2 months, respectively. The incidence of a QTcF interval > 500 ms ranged from 0.6% (1/161) - 2.1% (7/341) in patients receiving delamanid 200 mg total daily dose versus 0% (0/160) - 1.2% (2/170) of patients receiving placebo + OBR, while the incidence of QTcF change from baseline > 60 ms ranged from 3.1% (5/161) - 10.3% (35/341) in patients receiving delamanid 200 mg total daily dose versus 0% (0/160) - 7.1% (12/170) in patients receiving placebo.

Palpitations
For patients receiving delamanid + OBR in the phase 2 and 3 trials, the frequency was 7.9% (frequency category common) in comparison to a frequency of 6.7% in patients receiving placebo + OBR.

Paediatric population

Based on a study (see section 5.1) in 37 paediatric patients aged 0 to 17 years, the frequency, type and severity of adverse reactions in children are expected to be the same as in adults.
Cases of hallucination have been reported predominantly in the paediatric population during post-marketing. The incidence of hallucination in clinical trials was common for children (5.4%) and adults (1%).
Cases of nightmare have been reported predominantly in the paediatric population during post-marketing.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions

4.9 Overdose

No cases of delamanid overdose have been observed in clinical trials. However, additional clinical data showed that in patients receiving 200 mg twice daily, i.e. total 400 mg delamanid per day, the overall safety profile is comparable to that in patients receiving the recommended dose of 100 mg twice daily. Albeit, some reactions were observed at a higher frequency and the rate of QT prolongation increased in a dose-related manner. Treatment of overdose should involve immediate measures to remove delamanid from the gastrointestinal tract and supportive care as required. Frequent ECG monitoring should be performed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycobacterials, drugs for treatment of tuberculosis, ATC code: J04AK06.

Mechanism of action

The pharmacological mode of action of delamanid involves inhibition of the synthesis of the mycobacterial cell wall components, methoxy-mycolic and keto-mycolic acid. The identified metabolites of delamanid do not show anti-mycobacterial activity.

Activity against specific pathogens

Delamanid has no in vitro activity against bacterial species other than mycobacteria.

Resistance

Mutation in one of the 5 coenzyme F420 genes is suggested as the mechanism for resistance against delamanid in mycobacteria. In mycobacteria, the *in vitro* frequencies of spontaneous resistance to delamanid were similar to those for isoniazid and were higher than those for rifampicin. Resistance to delamanid has been documented to occur during treatment (see section 4.4). Delamanid does not show cross-resistance with any of the currently used anti-tuberculosis medicinal products except pretomanid. *In vitro* studies have shown cross-resistance with pretomanid. This is likely to be due to delamanid and pretomanid being activated via the same pathway.

Susceptibility testing interpretive criteria

When 7H11 agar medium is used for drug susceptibility testing, the recommended epidemiological cut-off (ECOFF) and susceptibility testing interpretive criteria for delamanid are:
ECOFF: 0.016 mg/L
Clinical breakpoint: $S \leq 0.016$ mg/L; $R > 0.016$ mg/L
S = susceptible; R = resistant

Data from clinical studies

Delamanid has been evaluated in two, double-blind, placebo-controlled trials for the treatment of MDR-TB. The analyses of SCC were conducted on the modified intent to treat population which included patients who had positive cultures at baseline and the isolate was resistant to both isoniazid and rifampicin, i.e., had MDR-TB.

In the first trial (Trial 204), 64/141 (45.4%) patients randomised to receive delamanid 100 mg BID + OBR and 37/125 (29.6%) of patients randomised to receive placebo (PLC) + OBR achieved two-month sputum culture conversion (SCC) (i.e. growth of *Mycobacterium tuberculosis* to no growth over the first 2 months and maintained for 1 more month) ($p = 0.0083$). The time to SCC for the group randomised to 100 mg BID was also found to be faster than for the group randomised to receive placebo + OBR ($p = 0.0056$).

In the second trial (Trial 213), delamanid was administered orally at 100 mg BID as an add-on therapy to an OBR for 2 months followed by 200 mg once daily for 4 months. The median time to SCC was 51 days in the delamanid + OBR group compared with 57 days in the PLC + OBR group ($p = 0.0562$ using the stratified modified Peto-Peto modification of Gehan's Wilcoxon rank sum test). The proportion of patients achieving SCC (sputum culture conversion) after the 6-month treatment period was 87.6% (198/226) in the delamanid + OBR treatment group compared to 86.1% (87/101) in the placebo + OBR treatment group ($p = 0.7131$).

All missing cultures up to the time of SCC were assumed to be positive cultures in the primary analysis. Two sensitivity analyses were conducted - a last-observation-carried-forward (LOCF) analysis and an analysis using 'bookending' methodology (which required that the previous and subsequent cultures were both observed negative cultures to impute a negative result, otherwise a positive result was imputed). Both showed a 13-day shorter median time to SCC in the delamanid + OBR group ($p = 0.0281$ for LOCF and $p = 0.0052$ for 'bookending').

Delamanid resistance (defined as MIC $\geq$ 0.2 µg/mL) has been observed at baseline in 2 of 316 patients in Trial 204 and 2 of 511 patients in Trial 213 (4 of 827 patients [0.48%]). Delamanid resistance emerged in 4 of 341 patients (1.2%) randomised to receive delamanid for 6 months in Trial 213. These four patients were only receiving two other medicinal products in addition to delamanid.

Paediatric population

The pharmacokinetics, safety and efficacy of delamanid in combination with a background regimen (BR) were evaluated in trial 242-12 -232 (10 days pharmacokinetics) followed by trial -233 (pharmacokinetics, efficacy and safety), both single-arm, open-label trials, which included 37 patients who had a median age of 4.55 years (range 0.78 to 17.60 years), 25 (67.6%) were Asian and 19 (51.4%) were female.
Paediatric patients were enrolled in four groups:
Group 1: 12 to 17 years (7 patients), group 2: 6 to 11 years (6 patients), group 3: 3 to 5 years (12 patients) and group 4: 0 to 2 years (12 patients). The overall mean baseline body weight of subjects was 19.5 kg and in groups 1, 2, 3, and 4 the mean body weights were 38.4, 25.1, 14.8, and 10.3 kg, respectively.

The patients had confirmed or probable MDR-TB infection and were to complete 26 weeks of treatment with delamanid + OBR, followed by OBR only in accordance with the WHO recommendation. Patients in groups 1 and 2 received film-coated tablets. The delamanid dose in group 1 was 100 mg twice daily and 50 mg twice daily in group 2. The doses administered were higher than the currently recommended weight-based dosage in the paediatric population. Patients in groups 3 and 4 received dispersible tablets. This paediatric formulation is not bio-equivalent with the film-coated tablets. Patients in group 3 were administered 25 mg twice daily and patients in group 4 were administered doses between 10 mg twice daily and 5 mg once daily based on body weight. The doses administered in group 4 were below the currently recommended weight-based dosage in the paediatric population.
A population PK analysis was performed on data from the 2 paediatric trials to determine the doses in paediatric subjects which would provide delamanid exposures similar to those observed in adult subjects with MDR-TB. Data in children with a body weight of less than 10 kg were too limited to determine doses for that patient population.

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited.

5.2 Pharmacokinetic properties

Absorption

Oral bioavailability of delamanid improves when administered with a standard meal, by about 2.7-fold compared to fasting conditions. The peak plasma concentrations are reached in approximately 4 hours post-dose, regardless of food intake.

Distribution

Delamanid highly binds to all plasma proteins with a binding to total proteins of $\geq$ 99.5%. Delamanid has a large apparent volume of distribution (Vz/F of 2 100 L).

Biotransformation

Delamanid is primarily metabolised in plasma by albumin and to a lesser extent by CYP3A4. The complete metabolic profile of delamanid has not yet been elucidated, and there is a potential for drug interactions with other co-administered medicinal products, if significant unknown metabolites are discovered. The identified metabolites do not show anti-mycobacterial activity but some contribute to QTc prolongation, mainly DM-6705. Concentrations of the identified metabolites progressively increase to steady state after 6 to 10 weeks.

Elimination

Delamanid disappears from plasma with a $t_{1/2}$ of 30 to 38 hours. Delamanid is not excreted in urine.

Linearity/non-linearity

Delamanid plasma exposure increases less than proportionally with increasing dose.

Special populations

Paediatric population
During treatment with the recommended delamanid doses to adolescents and children with a body weight of at least 10 kg (see section 4.2), similar plasma exposure were obtained as in adults.

Patients with renal impairment
Less than 5% of an oral dose of delamanid is recovered from urine. Mild renal impairment (50 mL/min < CrCLN < 80 mL/min) does not appear to affect delamanid exposure. Therefore no dose adjustment is needed for patients with mild or moderate renal impairment. It is not known whether delamanid and metabolites will be significantly removed by haemodialysis or peritoneal dialysis.

Patients with hepatic impairment
No dose adjustment is considered necessary for patients with mild hepatic impairment. Delamanid is not recommended in patients with moderate to severe hepatic impairment.

Elderly patients (≥ 65 years)
No patients of ≥ 65 years of age were included in clinical trials.

5.3 Preclinical safety data

Non-clinical data reveal no specific hazard for humans based on conventional studies for genotoxicity and carcinogenic potential. Delamanid and/or its metabolites have the potential to affect cardiac repolarisation via blockade of hERG potassium channels. In the dog, foamy macrophages were observed in lymphoid tissue of various organs during repeat-dose toxicity studies. The finding was shown to be partially reversible; the clinical relevance of this finding is unknown. Repeat-dose toxicity studies in rabbits revealed an inhibitory effect of delamanid and/or its metabolites on vitamin K-dependent blood clotting. In rabbits reproductive studies, embryo-fetal toxicity was observed at maternally toxic dosages. Pharmacokinetic data in animals have shown excretion of delamanid/metabolites into breast milk. In lactating rats, the C_{max} for delamanid in breast milk was 4-fold higher than that of the blood. In juvenile toxicity studies in rats, all delamanid treatment-related findings were consistent with those noted in adult animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Hypromellose phthalate
Povidone

all-rac-α-Tocopherol
Cellulose, microcrystalline
Sodium starch glycolate (type A)
Carmellose calcium
Silica, colloidal hydrated
Magnesium stearate
Lactose monohydrate

Film coating
Hypromellose
Macrogol 8000
Titanium dioxide
Talc
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store below 30 ºC. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Aluminium/Aluminium blister:
48 tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Manufactured by:

Manufacturer for spray-dried powder
Gohkakizawa Factory Fuji Chemical Industries Co., Ltd. 1 Gohkakizawa, Kamiichi-machi, Nakaniikawa-gun Toyama, Japan.

Manufacturer of Tablet.
Otsuka Pharmaceutical Co., Ltd. Tokushima Itano Factory 13, Minami, Shishitoki, Matsutani, Itano-cho, Itano-gun Tokushima ,Japan.

Primary and Secondary Packaging

R-Pharm Germany GmbH. Heinrich-Mack-Straße 35, Illertissen, Germany

Imported by:

Otsuka Thai Otsuka Pharmaceutical Co., Ltd.

Bangkok, Thailand

Under license from:

Otsuka Pharmaceutical Co., Ltd.

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